American Psychologist

ISSN: 0003-066X

2022, Vol. 77, No. 6, 760–769
https://doi.org/10.1037/amp0001031

Resting-State Functional Connectome Predicts Individual Differences in Depression During COVID-19 Pandemic

Yu Mao[1, 2], Qunlin Chen[2], Dongtao Wei[2], Wenjing Yang[2], Jiangzhou Sun[2], Yaxu Yu[2], Kaixiang Zhuang[2], Xiaoqin Wang[2], Li He[2], Tingyong Feng[2], Xu Lei[2], Qinghua He[2], Hong Chen[2], Shukai Duan[3], and Jiang Qiu[2]

[1] College of Computer and Information Science, School of Software, Southwest University

[2] Faculty of Psychology, Key Laboratory of Cognition and Personality of the Ministry of Education, Southwest University

[3] College of Artificial Intelligence, Southwest University

Stressful life events are significant risk factors for depression, and increases in depressive symptoms have been observed during the COVID-19 pandemic. The aim of this study is to explore the neural makers for individuals' depression during COVID-19, using connectome-based predictive modeling (CPM). Then we tested whether these neural markers could be used to identify groups at high/low risk for depression with a longitudinal dataset. The results suggested that the high-risk group demonstrated a higher level and increment of depression during the pandemic, as compared to the low-risk group. Furthermore, a support vector machine (SVM) algorithm was used to discriminate major depression disorder patients and healthy controls, using neural features defined by CPM. The results confirmed the CPM's ability for capturing the depression-related patterns with individuals' resting-state functional connectivity signature. The exploration for the anatomy of these functional connectivity features emphasized the role of an emotion-regulation circuit and an interoception circuit in the neuropathology of depression. In summary, the present study augments current understanding of potential pathological mechanisms underlying depression during an acute and unpredictable life-threatening event and suggests that resting-state functional connectivity may provide potential effective neural markers for identifying susceptible populations.

Public Significance Statement

The primary aim of this study is to exploit and validate individualized neural markers to facilitate the prediction of depressive emotions during COVID-19. The predictive model worked well in the prediction of depression and was successfully validated in an

This article was published Online First July 21, 2022.

Yu Mao https://orcid.org/0000-0002-5754-3773

Qunlin Chen https://orcid.org/0000-0002-7396-1297

Yu Mao was supported by the Chongqing Social Science Planning Project (Grants 2021BS093). Jiang Qiu was supported by the National Natural Science Foundation of China (Grants 31771231 and 32071070), the Chang Jiang Scholars Program, the National Outstanding Young People Plan, and the Chongqing Talent Program. Dongtao Wei was supported by the Natural Science Foundation of Chongqing (Grants cstc2019jcyj-msxmX0520 and cstc2020jcyj-msxmX0299), the Fundamental Research Funds for the Central Universities (Grant SWU119007), and the Social Science Planning Project of Chongqing (Grant 2018PY80). Shukai Duan was supported by the National Key Research and Development Program of China (Grant 2018YFB1306600), the National Natural Science Foundation of China (Grants 62076207, 62076208, and U20A20227), and the Science and Technology Plan Program of Yubei District of Chongqing (Grant 2021-17). The authors thank all participants who volunteered for this study. The authors have no conflict of interest to disclose.

Yu Mao played a lead role in validation, visualization, and writing of original draft, and an equal role in formal analysis, investigation, and methodology. Qunlin Chen played a supporting role in resources. Dongtao Wei played a supporting role in project administration. Wenjing Yang played a supporting role in resources. Jiangzhou Sun played a supporting role in resources. Yaxu Yu played a supporting role in resources. Kaixiang Zhuang played a supporting role in resources. Xiaoqin Wang played a supporting role in resources. Li He played a supporting role in resources. Tingyong Feng played a supporting role in funding acquisition and resources. Xu Lei played a supporting role in funding acquisition and resources. Qinghua He played a supporting role in funding acquisition and resources. Hong Chen played a supporting role in funding acquisition and resources. Shukai Duan played a supporting role in methodology and writing of review and editing. Jiang Qiu played a lead role in supervision and a supporting role in funding acquisition and resources.

The connectome-based predictive modeling (https://github.com/YaleMRRC/CPM) is used to train the predictive model (Finn et al., 2015; Shen et al., 2017). The Library for Support Vector Machines (LIBSVM; https://www.csie.ntu.edu.tw/~cjlin/libsvm/) is used to implement support vector regression (Chang & Lin, 2011). The data are available upon request.

Correspondence concerning this article should be addressed to Jiang Qiu, Faculty of Psychology, Key Laboratory of Cognition and Personality of the Ministry of Education, Southwest University, Beibei District, Chongqing 400715, China or Shukai Duan, College of Artificial Intelligence, Southwest University, Beibei District, Chongqing 400715, China. Email: qiuj318@swu.edu.cn or duansk@swu.edu.cn

independent sample. The results indicated two main functional connectivity patterns in the prediction of depression, including an emotion-regulation circuit and an interoceptive circuit. We believe these findings can be informative for mental health practitioners to identify and help potential populations at risk for emotional disorder during COVID-19.

Keywords: COVID-19, depression, functional connectivity, neural markers

Supplemental materials: https://doi.org/10.1037/amp0001031.supp

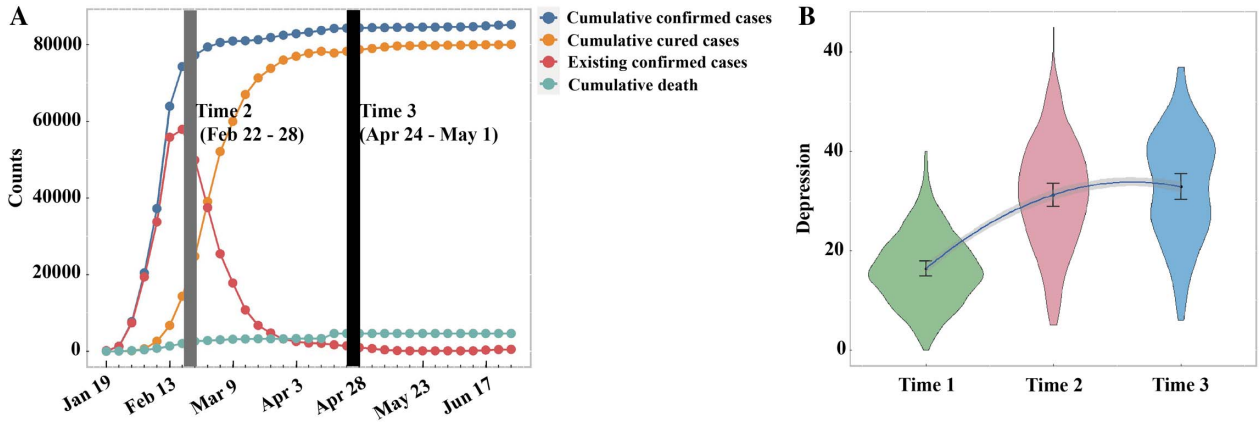
The COVID-19 pandemic is causing mental health problems around the world (Hossain et al., 2020; Talevi et al., 2020). Previous studies have demonstrated that the fear of infection and death can lead to feelings of helplessness and desperation (Wang et al., 2020). Specifically, during the severe acute respiratory syndrome (SARS) pandemic, both infected and noninfected communities reported a significant increase in psychiatric symptoms (Sim et al., 2010). Although most people do not develop major depression disorder (MDD) after exposure to negative life events, there are abundant evidences supporting the strong association between stressful life events and the onset (or symptom severity) of depression (Hammen, 2005; Kendler et al., 2001). The diathesis–stress model suggests that preexisting vulnerabilities increase the risk of psychiatric disorders only under exposure to stressors (Eberhart et al., 2011). Both retrospective and prospective studies have supported this view by revealing stressful life events as robust predictors for depression (Kendler et al., 2001; Van Praag et al., 2004). In summary, based on the suggested causality between stressful life events and depression, it is reasonable to speculate that individuals' depression would increase as the COVID-19 pandemic surges.

Aberrant brain structure or communication between large-scale functional brain networks has been detected in MDD patients, and most of these studies suggested brain areas including the frontal cortex and subcortical areas, such as the amygdala and hippocampus, as underlying the neuropathology of MDD (Kaiser et al., 2015; Schmaal et al., 2016). Despite the neural basis of depression having been widely investigated both in clinical and nonclinical samples (Wang et al., 2015, 2012; Wei et al., 2020), the neural underpinning of depressive symptoms caused by a particular stressful life event (like the COVID-19 pandemic) is poorly understood. As a data-driven approach, connectome-based predictive modeling (CPM; Finn et al., 2015; Shen et al., 2017) adopted multivariate pattern analysis based on whole-brain resting-state functional connectivity (FC). In particular, this technique utilizes the rich information provided by magnetic resonance imaging (MRI) data and works well in the generalization of results (Yoo et al., 2018).

Although everyone suffered from the COVID-19 pandemic, the ability to cope with stressful life events varies among human beings (Zong et al., 2010). Individual differences in vulnerability to depression might be magnified by the COVID-19 pandemic, that is, an individual with poor coping ability might develop a higher level of depression. Individuals' depression after a particular negative life event has not been studied in a highly homogeneous group. Having a large sample of MRI data and longitudinal behavior data during the pandemic is unique and valuable in this sense. Exploring neural markers for depression across the pandemic could not only contribute to the identification of the vulnerable groups especially sensitive to stressful events but also facilitate the comprehension of the neuropathology underlying stress-induced depression.

The present study is designed to investigate the neural makers for individuals' depression under COVID-19. Baseline depression was measured in 2019 after MRI scanning (Time 1), and depression during the pandemic was measured on February 22–28 (Time 2, the peak point of the COVID-19 pandemic in China) and April 24–May 1 (Time 3) in 2020 (Figure 1A). First, a linear mixed-effect (LME) model was used to estimate the changing trajectories of depression across the pandemic. Second, a predictive model was trained to predict individuals' depression at Time 2 based on the large sample of resting-state functional Magnetic resonance imaging (fMRI) data. Although we found the FC features that could predict individuals' depression during the COVID-19 pandemic, it is unclear whether these features could be used to identify vulnerable groups susceptible to depression in response to stressful life events. Thus, we divided the sample into two groups according to the FC strengths of these features, and LME was implemented to test a group difference in the intercept (main effect of group) as well as the trajectory or slope of changes over time (Time × Group interaction). We hypothesized that the high-risk group would suffer higher increases of depression across the pandemic. Third, to verify the generalizability of CPM, we applied the predictive model to an independent dataset. Finally, we tested whether these FC features could be used to classify MDD patients and healthy controls. Thus, the FC features were extracted and used as input patterns to a support vector machine (SVM) classifier.

Figure 1
The Changes of Depression Scores During COVID-19 Pandemic



Note. (A) The development of COVID from January 19, 2019 to June 17, 2020, in China. Individuals' depression was measured on February 22–28 (gray line: the peak point of the pandemic) and April 24–May 1 (black line: the time when the pandemic was under control) separately. (B) Overall trend for the changes of depression during the pandemic. See the online article for the color version of this figure.

Accuracy, specificity, and sensitivity were used to evaluate the classification performance.

Method

Participants

BBP Sample

The data set is part of an ongoing project: Behavioral-Brain Research Project of Chinese Personality (BBP). The participants were recruited for this project and completed the MRI scanning between September and December 2019. Among them, 901 participants were recontacted for the behavioral test during the COVID-19 pandemic. Six hundred four participants (177 males, aged 17–26 years) finished the MRI scanning and the behavioral test. All participants were right-handed, and none of them had a history of psychiatric or neurological illnesses. Every one of the participants provided the informed consent document prior to the experiment and was compensated with money at the end of the study. The ethical approval of this study was granted by the Ethics Committee of Southwest University, and all procedures involved were in accordance with the sixth revision of the Declaration of Helsinki. Baseline depression was assessed after the MRI scanning. Time 2 depression was measured on February 22–28, 2020 and Time 3 depression was measured on April 24–May 1, 2020, using the Self-Rating Depression Scale (SDS; Zung, 1965). Details of SDS are presented in Supplemental Information Method s2.

Validation Sample

The participants of the validation sample were college students at Southwest University. All participants were right-handed, and none of them had a history of psychiatric or neurological illnesses. Depression during the COVID-19 pandemic was measured on May 2, 2020, using the center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). Two hundred eighty-two participants completed the behavior measures but only 32 participants (5 males, aged 18–21 years) completed the MRI scanning before the outbreak of COVID-19.

Major Depression Disorder Sample

Two hundred eighty-two MDD (99 males, aged 18–60 years) outpatients and 254 healthy controls (88 males, aged 18–60 years) were recruited in this sample. Resting-state functional MRI scanning was completed at Southwest University. All the participants completed the diagnostic interview by experienced doctors using the structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, for axis I disorders. In this study, the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used to measure the depression severity of the participants. The study was approved by the institutional review board of Chongqing Medical University for the protection of human subjects and was performed in accordance with the Declaration of Helsinki. All participants signed written informed consent to participate.

Data Acquisition and Preprocessing

For the resting-state fMRI scan, participants were instructed to keep their eyes closed and rest without thinking about anything in particular. Whole-brain functional images were acquired on a 3.0 T Siemens Trio MRI scanner. All fMRI data were preprocessed using Statistical Parametric Mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm) and a data processing assistant for resting-state fMRI (DPARSF;

Chao-Gan & Yu-Feng, 2010). The processing procedure included the following steps: removal of the first 10 EPI scans, correction of slice timing and head motion, spatial normalization, nuisance signal regression, data scrubbing, spatial smoothing, and band-pass filtering. Details are provided in Supplemental Information Method s1.

CPM-Based Prediction

CPM was recently developed to predict individual differences in personality traits and cognitive abilities (Finn et al., 2015; Rosenberg et al., 2016), via functional connectivity derived from fMRI. First, the average blood-oxygenation-level-dependent time series of the resting-state fMRI data were extracted based on the Human Brainnetome Atlas (Fan et al., 2016). Then Pearson's correlation was used to construct an individual-level functional connectivity matrix, and the correlation coefficients were Fisher's r-to-z transformed. During the feature selection step, the partial correlation was performed to calculate the correlation between functional connectivity and depression scores (Time 2), controlling for age, sex, and mean framewise displacement power. Edges were chosen based on a predefined threshold ($p < .00001$) and separated into a positive network and a negative network. We also performed CPM with other thresholds and presented the results in the Supplemental Information. The positive and negative network strengths were obtained by summing the edges within the network. Then, a linear model was trained based on the training data, with positive and negative networks computed separately and the model was validated using leave-one-out cross-validation. Prediction performance was assessed by correlating predicted scores and observed scores. In addition, the significance of the predictive model was assessed with a permutation test. We randomly shuffled depression scores 1,000 times and ran the above prediction pipeline for each time to obtain a null distribution of the Pearson correlation coefficient between the predicted and actual scores. The number of the null r values was greater than or equal to the observed r value plus one and then divided by 1,001 providing an estimated p value. Because the prediction networks were slightly different in each iteration of the cross-validation, the common edges from all the negative networks were extracted to construct the final predictive model. Finally, to test the generalization of the predictive model, we applied it to an independent validation sample.

Statistical Analysis

Linear and quadratic LME were used to evaluate the changing trajectories of individuals' depression across the COVID-19 pandemic. LME estimates the fixed effect of time on individuals' depression while including within-person variation as nested random effects in the model. This is done to control for individual subject effects and correlation of the data inherent to longitudinal analysis. The null, linear and quadratic models were as follows:

1. Null model: $\text{Depression}_{ij} = \text{Intercept}_{0i} + \varepsilon$,
2. Linear model: $\text{Depression}_{ij} = \text{Intercept}_{0i} + \alpha\,(\text{time}) + \varepsilon$,
3. Quadratic model: $\text{Depression}_{ij} = \text{Intercept}_{0i} + \alpha\,(\text{time}) + \beta\,(\text{time}^2) + \varepsilon$,

where Depression_{ij} represents the level of depression at the jth time point for the ith participant, the intercept_{0i} represents the grand mean at baseline, α and β represent the effects of each fixed term, and ε is the residual error and reflects within-person variance. All models also included a random intercept for each participant. Likelihood-ratio tests and Akaike information criterion (AIC) were used to compare the models and to determine which had the best fit. All models were tested against a null model that included only the intercept term, but not the fixed effect of time. The model with the lowest AIC that was also significantly different from the less complex model as determined by the likelihood-ratio test was chosen as the best fit model (e.g., the linear model had to have a lower AIC and be significantly different from the null model; the quadratic model had to have a lower AIC and be significantly different from both the null model and linear model).

Then we tested whether these neural markers could be used to identify groups at high/low risk of depression. We expected the high-risk group would suffer higher increases of depression during the pandemic. We divided the sample into high-/low-risk groups according to the sum of the FC strengths in the predictive model. Specifically, the scores were normalized and the low FC group contained individuals with z score < 0, while the high FC group contained individuals with z score ≥ 0. Then, LME was used to estimate the group difference (low-risk group vs. high-risk group) in changing trajectories of depression across the pandemic. Group, time, as well as a Time × Group interaction were included in the model.

Classification Framework

A polynomial kernel-based nu-support vector machine classifier based on the LIBSVM library (Chang & Lin, 2011) was applied to evaluate the classification performance of the FC features with the leave-one-out cross-validation procedure. The FC features were selected according to the CPM results and used as input patterns for the SVM classifier. The performance of the classifier was assessed using the

Table 1
Demographic Data of the BBP Sample

Index	Age		Depression T1	Depression T2	Depression T3
	Female	Male	All (male)	All (male)	All (male)
N	628	273	795 (241)	901 (273)	737 (226)
M	19.45	19.26	36.09	50.50	51.43
SD	0.78	1.01	6.86	10.41	11.10

Paired *t* test	Depression T1 versus T2 (N = 795)	Depression T2 versus T3 (N = 737)	Depression T1 versus T3 (N = 651)
t value	−44.804	−2.912	−38.438
p value	<.001	.004	<.001

Note. BBP = Behavioral-Brain Research Project of Chinese Personality.

sensitivity, specificity, and classification accuracy based on the results of the cross-validation.

Results

Demographics and Behavior Results

The demographic data of the BBP sample are presented in Table 1. Paired *t* test suggested that there were significant increases of depression from Time 1 to Time 3 ($P_{T1\_T2} < .001$, $P_{T2\_T3} = .004$, $P_{T1\_T3} < .001$, see Table 1). For demographic data of other samples, please see Table s1 in Supplemental Information. LME was used to estimate the trajectory of depression and the results suggested that the best model is the quadratic model (see Table 2, Figure 1B).

CPM Results

CPM results indicated that the negative network, but not the positive network, could predict individuals' depression during the COVID-19 pandemic ($r = 0.179$, $p = 9.3 \times 10^{-6}$, Figure 2C, Table s2). It is common that depression is associated with emotional hypo-arousal, which was accompanied by hypo-connectivity between the frontal cortex and subcortical regions (Cheng et al., 2018; Rolls et al., 2019; Tang et al., 2013). Thus, the subsequent analysis was performed based on the negative network. To evaluate the chance level for the predictive power of the model, we performed 1,000-run permutation tests and the result survived the permutation test with resampling to estimate the changed null distribution for hypothesis testing ($p = .006$). We also presented the results of other thresholds of CPM in the Supplemental Information Figure s1.

External Validation

We used an independent validation data set to test the generalizability of the predictive model, and the results indicated that the model could predict individuals' depression in the validation sample ($r = 0.407$, $p = .021$, Figure 2D).

Anatomical Distribution of Edges Within the Predictive Model

We explored the anatomical distribution of edges in the predictive model and two main FC patterns were revealed (see Figure 2A, B). The first pattern was involved in emotion regulation, and comprised the brain regions of the cortical-thalamus-limbic system, especially the frontal cortex's FC with the amygdala and parahippocampal gyrus (Albaugh et al., 2013; Banks et al., 2007; Ramanathan et al., 2018; Taylor & Liberzon, 2007). The second pattern related to interoception was involved in the FC between the insula and frontal cortex (Caseras et al., 2013; Hassanpour et al., 2018). The brain regions involved in the negative prediction

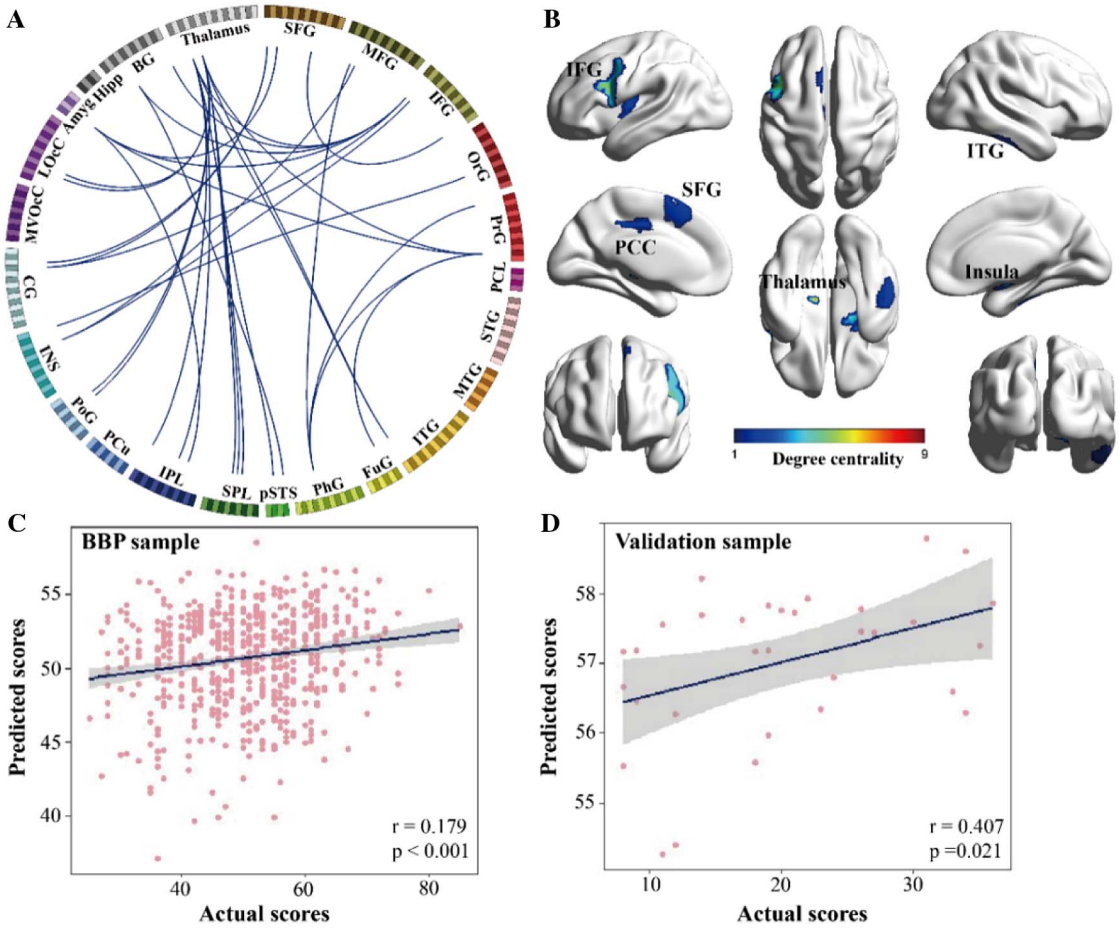
Table 2
Linear and Quadratic Linear Mixed-Effect Models Were Used to Determine Best-Fit Model for Depression Changing Under COVID-19

Best-fit model for depression changing during COVID-19 pandemic	Model	AIC	Log-likelihood	Test	Likelihood ratio	*p* value
Null model	1	17,921	−8957.40			
Linear model	2	17639.11	−8813.56	2 versus 1	−110.44	<.0001
				2 versus 3	60.04	<.0001
Quadratic model	3	17510.38	−8748.19	3 versus 1	−170.48	<.0001

Note. AIC = Akaike information criterion.

Figure 2

Functional Connections Predicting Depression During the COVID-19 Pandemic



Note. (A) Ring plot displays the predictive network and (B) demonstrate the degree centrality of each ROI in the predictive network. (C and D) The correlation between the predicted value and actual value in BBP sample and validation sample. Amyg = amygdala; Hipp = hippocampus; BG = basal ganglion; SFG = superior frontal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; OrG = orbital-frontal gyrus; PrG = precentral gyrus; PCL = paracentral lobule; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FuG = fusiform gyrus; PhG = parahippocampal gyrus; pSTS = posterior superior temporal sulcus; SPL = superior parietal lobule; IPL = inferior parietal lobule; PCu = precuneus; PoG = postcentral gyrus; INS = insula; CG = cingulate gyrus; MVOcC = medioventral occipital cortex; LOcC = lateral occipital cortex; PCC = posterior cingulate cortex; CPM = connectome-based predictive modeling; BBP = Behavioral-Brain Research Project of Chinese Personality; ROI = region of interest. See the online article for the color version of this figure.

network are consistent with current studies of depression (Avery et al., 2014; Erk et al., 2010; Harshaw, 2015; Rive et al., 2013).

Group Difference in the Changing Trajectories of Depression

The LME model included time, group as well as Time × Group interaction to test the group difference in the intercept and slope. Overall, the high-risk group showed higher levels of depression compared with the low-risk group across the pandemic. Moreover, a significant Time × Group interaction was revealed by the model (see Table 3, Figure 3), indicating a steeper increase of depression in the high-risk group across the pandemic, compared with the low-risk group.

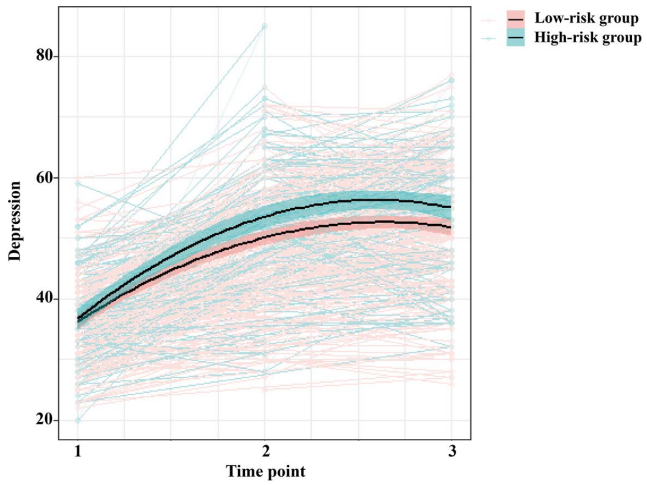
Table 3

Linear Mixed-Effect Model Estimated for Time, Group, and Time × Group of Depression

Parameters	Estimate	*SE*	*t* value	*p* value
Group (low vs. high)	−6.07	2.59	2.34	.019
Time	30.00	2.03	14.77	<.0001
Time^2	−5.56	0.51	−10.95	<.0001
Time × Group (low vs. high)	7.45	2.88	2.58	.009
Time^2 × Group (low vs. high)	−1.86	0.72	−2.58	.010

Note. Group was coded as a factor.

Figure 3
Changing Trajectories for Depression During the COVID-19 Pandemic



Note. The orange line represents the low-risk group and the green line represents the high-risk group. See the online article for the color version of this figure.

Classification Results

To test whether the features of the predictive model could distinguish MDD patients from healthy controls, a polynomial SVM classifier was used to evaluate the classification performance. The results showed an overall classification accuracy of 83%, with a sensitivity of 90% and a specificity of 68%. The weights of the FC features in SVM classification are presented in Figure s2, suggesting strong discriminative power of brain areas including the parahippocampal gyrus, amygdala, thalamus, insula, middle frontal gyrus (MFG), middle temporal gyrus (MTG), and inferior temporal gyrus (ITG).

Discussion

To the best of our knowledge, this is the first study to explore the neural mechanisms underlying individual differences in depression during the COVID-19 pandemic, a topic of great interest and significance, with a large sample (n = 604). First, we revealed the functional connectivity pattern which could predict individual differences in depression across the pandemic and demonstrated successful generalizability of the predictive model on a validation sample. Second, LME suggested the quadratic model as the best fit model to describe the changing trajectory of individuals' depression. The longitudinal data revealed that the high-risk group suffered steeper increases of depression during the pandemic. Finally, SVM-based classification suggested a good prediction accuracy of the FC features in discriminating MDD patients and healthy controls. These findings provide neural markers for identifying depression-prone individuals and also provide information for psychological intervention.

Emotion-Regulation Circuit

Consistent with previous studies, our results emphasized the functional connectivity of the frontal-limbic system in the neuropathology of depression under stress (Luking et al., 2011). Clinical studies have highlighted that the crucial pathways of the frontal-limbic system are disrupted among MDD patients, accompanied by inefficient emotion-regulation processes in response to a stressful stimulus (Seminowicz et al., 2004). Empirical studies have elucidated reciprocal prefrontal cortex-amygdala communications during successful emotion regulation (Banks et al., 2007). In addition, altered connectivity of the parahippocampal gyrus might be associated with deficits in emotion-mediated memory formation observed in depression (Savitz & Drevets, 2009). These results suggest that the decreased frontal-limbic connectivity in an individual with higher levels of depression might be associated with emotion dysregulation.

Furthermore, this study revealed that another pivotal brain region associated with depression during the pandemic is the thalamus. The thalamus is involved in transferring sensory information from the external environment to diverse parts of the cerebral cortex where sensory information can be integrated systematically (Lanius et al., 2003). A previous study indicated that high emotional arousal can result in altered thalamic sensory processing (Salay et al., 2018). The interaction between the thalamus and cortical regions has been proved to be critical for attention and cognitive control (Schmitt et al., 2017). Thus, decreased thalamus-related FC might be implicated in altered sensory information transmission, which ultimately leads to disturbances in autonomic regulation in response to a stressful stimulus (Drevets et al., 2008).

Interoception Circuit

Functional connectivity between the frontal cortex and insula was also reported in the predictive model. Both neuropsychological and neuroimaging studies have suggested the role of the insula in interoceptive awareness (Critchley et al., 2004; Simmons et al., 2013). Aberrant connections between the insula and frontal cortex have been widely reported in neuroimaging studies of MDD (Drevets et al., 2008; Greicius et al., 2007). We proposed that depression is associated with decreased functional connectivity between the frontal cortex and insula, as well as the basal ganglia, which might indicate susceptibility to somatic and interoceptive dysfunction (Sheline et al., 2010).

The Change Trajectory of Depression Across COVID-19 Pandemic

The present study describes the changing trajectory of individuals' depression, that is, individuals' depression increased rapidly after the outbreak, and the growth rate slowly declined as the pandemic was brought under control.

LME results indicated that the high-risk group suffered higher levels and increments of depression across the pandemic. Acute and unexpected stressful life events will increase depressive symptoms; however, the intensity of the influence varies among people. These results imply that individuals susceptible to depression under stress can be identified based on a specific FC pattern. The predictive model contains brain regions involved in emotion regulation (cortical-limbic-thalamus system), suggesting high-risk groups might have more difficulty in dealing with stressful life events, due to the deficiency in their emotion-regulation circuits. Thus, it is reasonable to infer that emotion-regulation training might be helpful for high-risk individuals to cope with acute stress.

Discrimination of Major Depressive Disorder Patients and Healthy Controls

This study demonstrated that the features of CPM can reliably discriminate between MDD patients and healthy controls, which suggests that these FC features are among the neurobiological underpinnings of depression. The brain regions of the CPM networks, including the parahippocampal gyrus, amygdala, thalamus, insula, MFG, MTG, and ITG, have been widely suggested to be powerful in MDD classification (Cao et al., 2014; Guo et al., 2014; Zeng et al., 2012). In summary, these results demonstrated the shared neurobiological underpinning of depressive symptoms in normal people under stress and MDD patients, which also implicates stressful life events as important etiological factors for depression.

Limitations

The present study has several limitations. All participants were healthy college students, and their risk of being infected with COVID-19 was relatively low. Future work might validate these neural markers in patients infected with COVID-19. Furthermore, the present study only focused on individuals' depression, and a more comprehensive approach is needed to investigate neural markers for individuals' mental health during COVID-19. Also, exploration of protective factors for mental health under stressful life events is another valuable direction for future studies.

Conclusion

The present study demonstrated the role of an emotion-regulation circuit and an interoception circuit in the prediction of depression under stressful life events, with multiple data sets and a machine-learning predictive framework. These neural markers could also discriminate MDD patients from healthy controls. These findings augment the understanding of the pathological mechanism of depression under a stressful life event and suggested that resting-state functional connectivity may provide effective neural markers for identifying populations who are susceptible to depression after exposure to major stressful events.

References

Albaugh, M. D., Ducharme, S., Collins, D. L., Botteron, K. N., Althoff, R. R., Evans, A. C., Karama, S., Hudziak, J. J., Group, B. D. C., & the Brain Development Cooperative Group. (2013). Evidence for a cerebral cortical thickness network anti-correlated with amygdalar volume in healthy youths: Implications for the neural substrates of emotion regulation. *NeuroImage*, *71*, 42–49. https://doi.org/10.1016/j.neuroimage.2012.12.071

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., & Simmons, W. K. (2014). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological Psychiatry*, *76*(3), 258–266. https://doi.org/10.1016/j.biopsych.2013.11.027

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–312. https://doi.org/10.1093/scan/nsm029

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck depression inventory (BDI-II)*. Pearson.

Cao, L., Guo, S., Xue, Z., Hu, Y., Liu, H., Mwansisya, T. E., Pu, W., Yang, B., Liu, C., Feng, J., Chen, E. Y., & Liu, Z. (2014). Aberrant functional connectivity for diagnosis of major depressive disorder: A discriminant analysis. *Psychiatry and Clinical Neurosciences*, *68*(2), 110–119. https://doi.org/10.1111/pcn.12106

Caseras, X., Murphy, K., Mataix-Cols, D., López-Solà, M., Soriano-Mas, C., Ortriz, H., Pujol, J., & Torrubia, R. (2013). Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. *Human Brain Mapping*, *34*(5), 1220–1229. https://doi.org/10.1002/hbm.21503

Chang, C.-C., & Lin, C.-J. (2011). LIBSVM: A library for support vector machines. *ACM Transactions on Intelligent Systems and Technology*, *2*(3), 1–27. https://doi.org/10.1145/1961189.1961199

Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: A MATLAB toolbox for" pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience*, *4*, Article 13. https://doi.org/10.3389/fnsys.2010.00013

Cheng, W., Rolls, E. T., Qiu, J., Xie, X., Lyu, W., Li, Y., Huang, C.-C., Yang, A. C., Tsai, S.-J., Lyu, F., Zhuang, K., Lin, C. P., Xie, P., & Feng, J. (2018). Functional connectivity of the human amygdala in health and in depression. *Social Cognitive and Affective Neuroscience*, *13*(6), 557–568. https://doi.org/10.1093/scan/nsy032

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, *7*(2), 189–195. https://doi.org/10.1038/nn1176

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure & Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Eberhart, N. K., Auerbach, R. P., Bigda-Peyton, J., & Abela, J. R. Z. (2011). Maladaptive schemas and depression: Tests of stress generation and diathesis-stress models. *Journal of Social and Clinical Psychology*, *30*(1), 75–104. https://doi.org/10.1521/jscp.2011.30.1.75

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., & Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *The Journal of Neuroscience*, *30*(47), 15726–15734. https://doi.org/10.1523/JNEUROSCI.1856-10.2010

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). The human brainnetome atlas: A new brain atlas based on connectional architecture. *Cerebral Cortex*, *26*(8), 3508–3526. https://doi.org/10.1093/cercor/bhw157

Finn, E. S., Shen, X., Scheinost, D., Rosenberg, M. D., Huang, J., Chun, M. M., Papademetris, X., & Constable, R. T. (2015). Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nature Neuroscience*, *18*(11), 1664–1671. https://doi.org/10.1038/nn.4135

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., & Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, *62*(5), 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Guo, H., Cheng, C., Cao, X., Xiang, J., Chen, J., & Zhang, K. (2014). Resting-state functional connectivity abnormalities in first-onset unmedicated depression. *Neural Regeneration Research*, *9*(2), 153–163. https://doi.org/10.4103/1673-5374.125344

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*(1), 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Harshaw, C. (2015). Interoceptive dysfunction: Toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychological Bulletin*, *141*(2), 311–363. https://doi.org/10.1037/a0038101

Hassanpour, M. S., Simmons, W. K., Feinstein, J. S., Luo, Q., Lapidus, R. C., Bodurka, J., Paulus, M. P., & Khalsa, S. S. (2018). The insular cortex dynamically maps changes in cardiorespiratory interoception. *Neuropsychopharmacology*, *43*(2), 426–434. https://doi.org/10.1038/npp.2017.154

Hossain, M. M., Tasnim, S., Sultana, A., Faizah, F., Mazumder, H., Zou, L., McKyer, E. L. J., Ahmed, H. U., & Ma, P. (2020). Epidemiology of mental health problems in COVID-19: A review. *F1000Research*, *9*, Article 636. https://doi.org/10.12688/f1000research.24457.1

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kendler, K. S., Thornton, L. M., & Gardner, C. O. (2001). Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *The American Journal of Psychiatry*, *158*(4), 582–586. https://doi.org/10.1176/appi.ajp.158.4.582

Lanius, R. A., Williamson, P. C., Hopper, J., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W. J., Gati, J. S., & Menon, R. S. (2003). Recall of emotional states in posttraumatic stress disorder: An fMRI investigation. *Biological Psychiatry*, *53*(3), 204–210. https://doi.org/10.1016/S0006-3223(02)01466-X

Luking, K. R., Repovs, G., Belden, A. C., Gaffrey, M. S., Botteron, K. N., Luby, J. L., & Barch, D. M. (2011). Functional connectivity of the amygdala in early-childhood-onset depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(10), 1027–41.e3. https://doi.org/10.1016/j.jaac.2011.07.019

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Ramanathan, K. R., Jin, J., Giustino, T. F., Payne, M. R., & Maren, S. (2018). Prefrontal projections to the thalamic nucleus reuniens mediate fear extinction. *Nature Communications*, *9*(1), Article 4527. https://doi.org/10.1038/s41467-018-06970-z

Rive, M. M., van Rooijen, G., Veltman, D. J., Phillips, M. L., Schene, A. H., & Ruhé, H. G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *37*(10 Pt. 2), 2529–2553. https://doi.org/10.1016/j.neubiorev.2013.07.018

Rolls, E. T., Cheng, W., Gong, W., Qiu, J., Zhou, C., Zhang, J., Lv, W., Ruan, H., Wei, D., Cheng, K., Meng, J., Xie, P., & Feng, J. (2019). Functional connectivity of the anterior cingulate cortex in depression and in health. *Cerebral Cortex*, *29*(8), 3617–3630. https://doi.org/10.1093/cercor/bhy236

Rosenberg, M. D., Zhang, S., Hsu, W.-T., Scheinost, D., Finn, E. S., Shen, X., Constable, R. T., Li, C.-S. R., & Chun, M. M. (2016). Methylphenidate modulates functional network connectivity to enhance attention. *The Journal of Neuroscience*, *36*(37), 9547–9557. https://doi.org/10.1523/JNEUROSCI.1746-16.2016

Salay, L. D., Ishiko, N., & Huberman, A. D. (2018). A midline thalamic circuit determines reactions to visual threat. *Nature*, *557*(7704), 183–189. https://doi.org/10.1038/s41586-018-0078-2

Savitz, J., & Drevets, W. C. (2009). Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide. *Neuroscience and Biobehavioral Reviews*, *33*(5), 699–771. https://doi.org/10.1016/j.neubiorev.2009.01.004

Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W. J., Vernooij, M. W., Ikram, M. A., Wittfeld, K., Grabe, H. J., Block, A., Hegenscheid, K., Völzke, H., Hoehn, D., Czisch, M., … Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, *21*(6), 806–812. https://doi.org/10.1038/mp.2015.69

Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., & Halassa, M. M. (2017). Thalamic amplification of cortical connectivity sustains attentional control. *Nature*, *545*(7653), 219–223. https://doi.org/10.1038/nature22073

Seminowicz, D. A., Mayberg, H. S., McIntosh, A. R., Goldapple, K., Kennedy, S., Segal, Z., & Rafi-Tari, S. (2004). Limbic-frontal circuitry in major depression: A path modeling metanalysis. *NeuroImage*, *22*(1), 409–418. https://doi.org/10.1016/j.neuroimage.2004.01.015

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(24), 11020–11025. https://doi.org/10.1073/pnas.1000446107

Shen, X., Finn, E. S., Scheinost, D., Rosenberg, M. D., Chun, M. M., Papademetris, X., & Constable, R. T. (2017). Using connectome-based predictive modeling to predict individual behavior from brain connectivity. *Nature Protocols*, *12*(3), 506–518. https://doi.org/10.1038/nprot.2016.178

Sim, K., Huak Chan, Y., Chong, P. N., Chua, H. C., & Wen Soon, S. (2010). Psychosocial and coping responses within the community health care setting towards a national outbreak of an infectious disease. *Journal of Psychosomatic Research*, *68*(2), 195–202. https://doi.org/10.1016/j.jpsychores.2009.04.004

Simmons, W. K., Avery, J. A., Barcalow, J. C., Bodurka, J., Drevets, W. C., & Bellgowan, P. (2013). Keeping the body in mind: Insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. *Human Brain Mapping*, *34*(11), 2944–2958. https://doi.org/10.1002/hbm.22113

Talevi, D., Socci, V., Carai, M., Carnaghi, G., Faleri, S., Trebbi, E., di Bernardo, A., Capelli, F., & Pacitti, F. (2020). Mental health outcomes of the CoViD-19 pandemic. *Rivista di Psichiatria*, *55*(3), 137–144. https://doi.org/10.1708/3382.33569

Tang, Y., Kong, L., Wu, F., Womer, F., Jiang, W., Cao, Y., Ren, L., Wang, J., Fan, G., Blumberg, H. P., Xu, K., & Wang, F. (2013). Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: A resting-state functional magnetic resonance imaging study. *Psychological Medicine*, *43*(9), 1921–1927. https://doi.org/10.1017/S0033291712002759

Taylor, S. F., & Liberzon, I. (2007). Neural correlates of emotion regulation in psychopathology. *Trends in Cognitive Sciences*, *11*(10), 413–418. https://doi.org/10.1016/j.tics.2007.08.006

Van Praag, H. M., de Kloet, E. R., & Van Os, J. (2004). *Stress, the brain and depression*. Cambridge University Press. https://doi.org/10.1017/CBO9780511544422

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S., & Ho, R. C. (2020). Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *International Journal of Environmental Research and Public Health*, *17*(5), Article 1729. https://doi.org/10.3390/ijerph17051729

Wang, K., Wei, D., Yang, J., Xie, P., Hao, X., & Qiu, J. (2015). Individual differences in rumination in healthy and depressive samples: Association with brain structure, functional connectivity and depression. *Psychological Medicine*, *45*(14), 2999–3008. https://doi.org/10.1017/S0033291715000938

Wang, L., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2012). A systematic review of resting-state functional-MRI studies in major depression. *Journal of Affective Disorders*, *142*(1–3), 6–12. https://doi.org/10.1016/j.jad.2012.04.013

Wei, D., Wang, K., Meng, J., Zhuang, K., Chen, Q., Yan, W., Xie, P., & Qiu, J. (2020). The reductions in the subcallosal region cortical volume and surface area in major depressive disorder across the adult life span. *Psychological Medicine*, *50*(3), 422–430. https://doi.org/10.1017/S0033291719000230

Yoo, K., Rosenberg, M. D., Hsu, W.-T., Zhang, S., Li, C. R., Scheinost, D., Constable, R. T., & Chun, M. M. (2018). Connectome-based predictive modeling of attention: Comparing different functional connectivity features and prediction methods across datasets. *NeuroImage*, *167*, 11–22. https://doi.org/10.1016/j.neuroimage.2017.11.010

Zeng, L.-L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., Zhou, Z., Li, Y., & Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: A multivariate pattern analysis. *Brain: A Journal of Neurology*, *135*(Pt. 5), 1498–1507. https://doi.org/10.1093/brain/aws059

Zong, J.-G., Cao, X.-Y., Cao, Y., Shi, Y.-F., Wang, Y.-N., Yan, C., Abela, J. R. Z., Gan, Y.-Q., Gong, Q.-Y., & Chan, R. C. K. (2010). Coping flexibility in college students with depressive symptoms. *Health and Quality of Life Outcomes*, *8*(1), Article 66. https://doi.org/10.1186/1477-7525-8-66

Zung, W. W. K. (1965). A self-rating depression scale. *Archives of General Psychiatry*, *12*(1), 63–70. https://doi.org/10.1001/archpsyc.1965.01720310065008

Received July 1, 2021
Revision received June 1, 2022
Accepted June 4, 2022 ■